PROGRESS REPORT 3:

"CORTICAL CONTROL OF NEUROPROSTHESES"

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This progress report reports on: 1- recent results of our feasibility demonstration of cortically controlled neuroprostheses in rats, 2- results of a mathematical/statistical investigation into methods for transforming the temporal patterning of cortical signals into a signal which matches the actual motor output, 3- progress in developing a neuroprosthesis paradigm for the monkey, 4- progress in developing a computer based real-time interface for neuroprostheses.

1- Neuroprosthetic Control from Forelimb Motor Cortex.

As briefly outlined in the previous two progress reports, we have implemented the plan outlined in the original RFP proposal to verify feasibility of NP control of an electromechanical arm in one dimension. In continuing investigations of this model, we have prepared two additional rats (NP5 and NP6).

NP5: NP5 was the best animal so far, in terms of accuracy and speed of its behavioral performance. Unfortunately, the quality and quantity of the single unit recordings was lacking, and so studies were carried out using multi-unit cluster recordings. Despite the relative failure of this animal, therefore, two important findings were made: First, we successfully showed that a good flow of usable task-related multiunit cluster information can be extracted from local areas of cortex when the electrodes are recorded differentially using a single common reference electrode. Second, the multiunit cluster activity has less variability over time than do individual neurons. We are currently investigating whether it is possible to use statistical techniques to extract specific movement information from multiunit cluster activity, and how the specificity of this information compares to that of single units.

NP6: We just implanted rat NP6 with two 16-electrode cortical recording arrays. One was implanted in the rat cortical area 4 (primary motor cortex) and the other was implanted in cortical area 6 (premotor cortex). Both of these areas have properties comparable to that in primates, in that both produce discrete limb movements upon electrical stimulation, and both contain neurons that discharge in relation to reaching movements of the forelimb. The premotor cortex, however, may ultimately be more useful for neuroprostheses because it is reportedly less strongly driven by somatosensory feedback than the primary motor cortex, and may therefore retain more activity after a spinal cord lesion.

2- Transforming the temporal domain of cortical signals into movements:

One of the predictable problems that we have encountered is that task related motor cortex neurons tend to discharge phasic bursts of activity just preceding and during the onset of active limb movement. Thus, there is a mismatch between the temporal patterning of cortical neural population activity vs. manipulandum displacement, which lasts longer. As a result, when we switch control of the robot arm away from the manipulandum and to the cortical activity integrator, the robot arm moves with a much more rapid time course. An interesting question, therefore, is how well cortical signals alone can (through appropriate mathematical transforms) predict the eventual trajectory of forelimb movement. We have recently completed a investigation into how well various statistical techniques can accomplish this transform. We are already using principal components analysis (PCA) to transform (in the purely spatial domain) the information from simultaneously recorded populations of neurons into a smaller number of significant components, one of which tends to be uniquely well mapped to the task-related activity. Therefore, rather than attempting to use data from the original population of neurons to simultaneously transform in both the spatial and temporal domains, we have applied various techniques to transform data from the first principal component (PC1), which typically summarizes most of the population activity. A number of mathematical approaches were used, including linear and nonlinear statistical functions, and various neural networks. The efficacy of all techniques was tested by measuring the correlation coefficient (R) between the transformed output function and the motor output signal (MOVE) measured during one typical experimental period of about 250 sec. The results are summarized below, and in figure 1, included here.

Regression functions: Regression is the generic statistical technique for matching one time series to another. Linear regression produced only a slight advantage over PC1 itself (R= .53 vs. .51) in its prediction of the motor output. Use of PC1 vs. the original 32 neuron data set was generally found to produce either the same, or better results. This was expected since PC1 had an eigenvalue of 11.9. It thus explained 37% of the total signal variance in the 32 neuron set, while separating out much of the remaining "noise" into other components. Next, nonlinear regression experiments were conducted. This was necessitated by the apparent nonlinear relationship between the PC1 and the motor signal. This was caused by the fact that the PC1 tended to lead the motor signal by up to several hundred msec. Thus, a simple approximation of a temporal transformation could be achieved by first finding the appropriate nonlinear function, and using it to derive a univariate regression equation. Both polynomial and piecewise-linear ("breakpoint") regression functions were derived. The piecewise-linear method proved slightly better than the polynomial function, achieving correlations (R) with the MOVE signal of .71 and .70 respectively. (When the piecewise linear method was allowed to use the MOVE signal to provide the breakpoints, an R of .9 was obtained, but this method would of course be unsuitable for a cortically controlled neuroprosthesis).

Tapped delay lines: A better way of using the temporal information embedded in the cortical signal (here using PC1), is to create tapped delay lines, i.e. sets of differentially lagged copies of the same signal, and then use them as variables in multivariate statistical procedures. Multivariate regression, discriminant analysis and canonical correlation analysis were used to derive transformation functions. All performed better than single nonlinear regression functions, but those derived using canonical correlation were best, achieving a .76 correlation with the MOVE signal. Multiple nonlinear regression and discriminant analysis were close, yielding R=.75 and .74 respectively. Discriminant functions were clumsy to use, however, in that they required dividing the MOVE signal into a set of discrete set of grouping variables. Without the tapped delay line, discriminant analysis fell apart, yielding an R=.28.

Neural Networks: We have also begun using neural network algorithms. The first one involved a single input, 3-layer feedforward perceptron with back-propagation learning. This network was essentially designed to find a single nonlinear regression function, but performed that task less well than those discussed above (R=.57, vs. .7 for nonlinear regression). As is often the case with neural networks, their theoretical superiority is compensated by the practical problems of setting them up properly. On the other hand, when the tapped delay line was used as input to the 3-layer feedforward perceptron, an excellent R=.77 was obtained. The best results (R=.86) were obtained with a 3-layer recurrent perceptron. A sample of these results are shown in the stripcharts in fig. 2, which show that the output of the neural network ("Predict Bar") was able to quite closely match the timing of the motor output function ("BAR") after a short period of learning (as measured by the decline of the error ("Cost") function to near 0.0, within about 50 sample periods. The recurrent network configuration is interesting in that it has a more biologically realistic structure: its hidden layer neurons have recurrent projections to other neurons in that layer. The nice (R=.86) result of using the recurrent network (using PC1 alone as an input) was not improved by adding more principal components (PCs 1-4). Moreover, when the raw data from the original 32 neurons was used instead of the PCs, the network fell apart and could not learn. Our conclusion, therefore, is that the best general approach to using cortical signals to reproduce actual movements will be use PCA to summarize the multi-neuron information into a much smaller variable set, and then to use recurrent neural networks to transform these generally phasic signals into longer duration signals which more closely approximate real motor outputs. Of course such empirical approaches may well be replaced in the future by models based on a sound understanding of how the motor system itself utilizes cortical signals to produce movement.

3- Monkey Recordings.

Progress has been made in Dr. Nicolelis' lab at Duke University in setting up appropriate experiments in the monkey. For the monkeys, we feel it is appropriate to set up a reaching task which will eventually allow the animal to move a robot arm in three dimensions. For this Dr. Nicolelis has obtained an tested a device which can be surface mounted on the monkey's arm to supply a continuous readout of joint positions in 3-space. This will provide the signal for forelimb directed movement of a robot arm from a water or food source to the monkeys mouth. Progress on the technical side toward developing this paradigm is further discussed below.

Meanwhile, more multi-neuron population recordings have been carried out in the somatosensory and motor cortices of a third owl monkey. Following these, we have submitted a manuscript (see enclosed) detailing the results of the first three monkeys.

Development of computer based real-time interface:

Following our initial proposal, Plexon Inc. (formerly Spectrum Scientific, Dallas, TX) has made substantial progress in developing a Windows NT version of their multineuron acquisition system, which now works in the Windows 3.1 and 95 operating systems. (Such systems are in place in the labs of Drs. Chapin, Nicolelis and Schwartz). Windows NT allows one to multi-thread different simultaneous tasks through multiple Pentium Pro processors on the same platform. After Plexon completes its NT version they will be able to provide the real-time unit discrimination information to another task which will control output to a motion device. Even though Windows NT is not a true real-time OS, it should work well within the time constraints in this application. Currently, the plan for controlling the motion devices is to utilize National Instrument's LabView-LabWindows package, which allows easy graphical programming of IO devices, and any conceivable transformation between them. Most of the available robotic systems interfaces provide drivers for control through LabView. This plan provides the laboratory investigators maximal flexibility in their experimentation with different schemes for transforming the cortical signals to motion system (of FNS) outputs. When and if this experimentation successfully identifies optimal transformation algorithms, they can be more compactly encoded into microelectronic systems with better real-time response.

TRANFORMING CORTICAL SIGNAL TO MOTOR OUTPUT

INPUT	METHOD	Correlation (R)
Neuron 1	none	.14
PC 1	none	.51
Neurons 1-32	Linear Regression	.53
PC1	Linear Regression	.58
PC1	Polynomial Regression	.70
PC1	Breakpoint Regression	.71
PC1	Discriminant Analysis	.28
PC1-TD*	Canonical Correlation	.76
PC1-TD*	Linear Regression	.68
PC1-TD*	Polynomial Regression	.75
PC1-TD*	Discriminant Analysis	.74
PC1	3-layer feedforward NN	.57
PC1-TD*	3-layer feedforward NN	.77
PC1	3-layer recurrent NN	.86
PC1-4	3-layer recurrent NN	.86
Neurons 1-32	3-layer recurrent NN	----

* Tapped delay line

Neural network prediction of BAR movement